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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/606,510	06/26/2003	Muthiah Manoharan	ISIC-0010-100/CHEM0004US	2562

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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 04/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/606,510	MANOHARAN, MUTHIAH	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 June 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 6-26-03.

Claims 1-68 are pending in the instant application.

Claim Objections

Claim 14 is objected to because of the following informalities: in line 3 of claim 14, the second "of" should perhaps be changed to –or--. In line 5 of claim 14, "olgiomeric" should perhaps be changed to –oligomeric--.. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-68 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The metes and bounds of the portions of the first and second oligomeric compounds that hybridize with each other cannot be determined (see *e.g.* lines 3-4 of cliam 1; line 3 of claim 23; line 2 claim 43) (*e.g.* is it a single base, two bases, ten bases or more that hybridize?). Adequate clarification is required.

The metes and bounds of the portion of the first oligomeric compound that is capable of hybridizing to a target nucleic acid cannot be determined (see e.g. lines 5-6

of claim 1; line 2 of claim 23; lines 3-4 of claim 43) (*e.g.* is it a single base, two bases, ten bases or more that hybridize to a target sequence?). Adequate clarification is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23-42, 61, 64 and 67 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to compositions comprising first and second oligomeric compounds and at least one protein comprising at least a portion of an RNA-induced silencing complex (RISC). The specification and claims do not adequately describe the distinguishing features or attributes concisely shared by the members of the genus comprising a *portion of an RNA-induced silencing complex*. The specification does not disclose adequate description of the genus comprising a *portion of an RNA-induced silencing complex*. No common structural attributes identify the members of the claimed genus, and distinguish members within the claimed genus from those outside of it. The genus encompasses a myriad of possible polypeptides or fragments of a complex without disclosing the structural requirements for activity. One of skill in the art would

reasonably conclude that the disclosure fails to provide a representative number of species to describe the characteristics of the genus claimed (which portions of this RISC provide for activity?). Thus, Applicant was not in possession of the claimed genus.

Claims 60-68 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the in vitro targeting of nucleic acid target sequences for inhibition of expression comprising the administration of the compounds or compositions claimed, does not reasonably provide enablement for the successful targeting and modulation of target gene expression in vivo comprising the administration of the broadly claimed oligonucleotide structures, nor does the specification provide enablement for the treatment or prevention of disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to compositions and methods for modulating target gene expression in vitro and in vivo, and methods for treating and preventing diseases or disorders, comprising the administration of compositions comprising a first and second oligomeric compound, wherein a portion of the first compound hybridizes with the second compound, and which first and second compounds are cross linked by photoactive coupling, or by disulfide, amide or other covalent cross linkages, and which composition optionally further comprises at least one protein comprising at least a portion of an RNA-induced silencing complex.

The state of the prior art and the predictability or unpredictability of the art. The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention over the scope claimed.

The following references are cited herein to illustrate the state of the art of treatment in organisms that involves the delivery of nucleic acid molecules to appropriate cells in an organism. Branch and Crooke teach that the in vivo (whole organism) application of nucleic acids is a highly unpredictable endeavor due to target accessibility and delivery issues. Crooke also points out that cell culture examples are generally not predictive of in vivo inhibition of target genes. (A. Branch, Trends in Biochem. Sci. 23: 45-50, document "BA" in IDS filed 11-17-03, *see* entire text for Branch; S. Crooke, Antisense Res. and Application, Chapter 1, pp. 1-50, especially at 34-36).

Likewise, Peracchi cautions investigators in the field of gene therapy about the problems of achieving in vivo efficacy using nucleic acid based approaches Peracchi cites stability and delivery obstacles that need to be overcome in achieving desired in vivo efficacy: "A crucial limit of ribozymes in particular, and of oligonucleotide-based drugs in general, lies in their intrinsically low ability to cross biological membranes, and therefore to enter the cells where they are supposed to operate...cellular uptake following systemic administration appears to require more sophisticated formulations... the establishment of delivery systems that mediate efficient cellular uptake and sustained release of the ribozyme remains one of the major hurdles in the field." (A. Peracchi et al, Rev. Med. Virol.,14: 47-64, especially at 51).

Agrawal et al also speak to the unpredictable nature of the nucleic acid based therapy field thus: "It is therefore appropriate to study each ... oligonucleotide in its own context, and relevant cell line, without generalizing the results for every oligonucleotide (S. Agrawal et al., Molecular Med. Today, 6: 72-81 at 80). Cellular uptake of oligonucleotides by appropriate target cells is another rate limiting step that has yet to be overcome in achieving predictable clinical efficacy using antisense." Both Chirila et al and Agrawal et al point to the current limitations which exist in our understanding of the cellular uptake of ... oligonucleotides in vitro and in vivo (see Agrawal et al especially at pages 79-80; *see* Chirila et al., Biomaterials, 23: 321-342 in its entirety, especially at 326-327 for a general review of the important and inordinately difficult challenges of the delivery of therapeutic oligonucleotides to target cells).

See Opalinska (Nature Reviews, Vol. 1, pages 503-514, 2002) for a review of the unpredictabilities associated with the in vivo efficacy of double stranded oligonucleotides for target gene inhibition: "Although conceptually elegant, the prospect of using nucleic acid molecules for treating human malignancies and other diseases remain tantalizing, but uncertain." (3rd full paragraph on p. 503). "...it is widely appreciated that the ability of nucleic acid molecules to modify gene expression in vivo is quite variable, ant therefore wanting in terms of reliability." (1st full paragraph on p. 511).

The following references are cited herein to illustrate that the delivery to a target cell in vitro or in vivo of candidate inhibitors such as polypeptides or small molecules is energy dependent and may require the presence of specific proteins that serve as

receptors and or channels. Derossi et al teach the ability of antennapedia homeodomain to translocate through biological membranes, but this ability is highly sequence dependent, and illustrates that delivery of polypeptides to target cells in vitro or in vivo is a rate limiting step for cell targeting and entry for most polypeptides (see D. Derossi et al. J. Biol. Chem. 269(14): 10,444-10,450, especially the abstract on p. 10,444, last paragraph of the introduction on p. 10,444; first full paragraph on p. 10,450: "Other polypeptides that cross biological membranes are those destined, after synthesis, to specific intracellular compartments such as the endoplasmic reticulum or the mitochondria... Passage through these intracellular membranes is energy-dependent and requires the presence of specific proteins that serve as receptors and/or channels. However, even in this rather well studied system, the actual mechanism of importation is not yet completely understood." For specific requirements of other, specialized polypeptides involved in cellular membrane penetration, see M. Pooga et al. FASEB J. 12: 67-77 for a discussion of the remarkable properties of transportan; see also G. Elliott et al, Cell 88 : 223-233 for the distinguishing features of Herpes virus structural protein and its role in intercellular trafficking).

The breadth of the claims and the quantity of experimentation required. The claims are broadly drawn to compositions and methods for modulating target gene expression in vitro and in vivo, and methods for treating and preventing any disease or disorder, comprising the administration of compositions comprising a first and second oligomeric compound, wherein a portion of the first compound hybridizes with the second compound, and which first and second compounds are cross linked by

photoactive coupling, or by disulfide, amide or other covalent cross linkages, and which composition optionally further comprises at least one protein comprising at least a portion of an RNA-induced silencing complex.

The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of accessible target sites, modes of delivery and formulations to target appropriate cells and /or tissues, whereby a representative number of the oligomeric structures claimed, including the broad genus comprising any number and type of crosslinkers between strands, and optionally further comprising any portion of a protein of an Rna-induced silencing complex, are delivered to the target cells or tissues in vivo in adequate amounts, and further whereby treatment and prophylactic effects are provided for any disease or disorder in a subject. Since the specification fails to provide any particular guidance for the successful targeting, delivery of a representative number of species of the broad genus of compounds and complexes claimed in vitro or in vivo, and further whereby target gene expression is inhibited and treatment and prophylactic effects are provided, and since determination of these factors is highly unpredictable, it would require undue experimentation to practice the invention over the scope claimed.

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided guidance in the specification toward a method of providing target gene inhibition in vitro or in vivo using a representative number of species within the broad genus of compounds claimed, nor of providing treatment or prophylaxis in vivo comprising the administration

of any agents. Applicants have not provided adequate written description for the compositions comprising a first and second oligomeric compound, wherein a portion of the first compound hybridizes with the second compound, and which first and second compounds are cross linked by photoactive coupling, or by disulfide, amide or other covalent cross linkages, and which composition optionally further comprises at least one protein comprising at least a portion of an RNA-induced silencing complex, nor the successful use of a representative number of species of the broad claimed to provide target gene inhibition in vitro or in vivo. The specification teaches various forms of crosslinked oligonucleotides, including conjugation of aryl azide photocrosslinkers, 2'-amine containing uridines for crosslinking, coupling of crosslinkers to amine-containing, abasic sites using sodium cyanoborohydride, and oxime and disulfide crosslinking between strands, whereby oligomeric crosslinking between a first and second oligonucleotide is obtained.

These experiments, however, are not representative of providing in vivo target gene inhibition, treatment or prophylactic effects in vivo. The generation of covalently crosslinked oligomeric structures is not representative of the ability to provide target gene inhibition or treatment effects in vivo using the synthesized compounds. In vivo results require undue experimentation, and cannot be generalized from a test tube (or cell culture) to an organism. One skilled in the art would not accept on its face the examples given in the specification of the synthesis of crosslinked siRNA structures as being correlative or representative of the successful in vivo modulation of target genes, nor of treatment or prevention of any disease or disorder in view of the lack of guidance

in the specification and known unpredictability associated with the ability to predict the efficacy of administering candidate biological agents to any organism. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with in vivo delivery and treatment effects provided by the claimed agents, and specifically regarding the instant compositions and methods claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-18, 21, 22-32, 35-38, 41-49, 52-55 and 58-65 are rejected under 35 U.S.C. 102(e) as being anticipated by Uhlmann et al (US 2003/0139585).

Uhlmann et al (US 2003/0139585) teach methods of inhibiting expression of a target gene in a cell in vitro comprising the administration of compositions including pharmaceutical compositions comprising double stranded oligonucleotides comprising complementary strands (sense and antisense) each comprising between 10 and 40 nucleotides, and which strands are covalently cross linked via disulfides or cross linked between heterocyclic bases, which oligomeric structures optionally comprise hairpins

and optionally further comprise space spanning polymers including polyethylene glycol moieties, and which cross linked oligomeric structures have improved nuclease resistance compared with un-cross linked structures, and which compositions optionally further comprise cellular proteins identified as RNA-induced silencing complexes, leading to the degradation of intrinsic sequence unspecific degradation of target sequences (see esp. bridging paragraph, pages 1-2 for disclosure of RISC complexes obtained from cellular extracts, see also the abstract, p. 1 right col., p. 2 right col., page 3 entire text, p. 6 left col., p. 7 left col., p. 8 left col., claims 1-27).

Claims 1-18, 21 and 22 are rejected under 35 U.S.C. 102(e) as being anticipated by Slattum et al (US 2004/0146867).

Slattum et al (US 2004/0146867) teach compositions comprising double stranded oligonucleotides comprising complementary strands (sense and antisense) each comprising between 10 and 40 nucleotides, and which strands are covalently cross linked via disulfides or amides, which oligomeric structures optionally comprise hairpins and optionally further comprise space spanning polymers comprising polyethylene glycol, and which cross linked oligomeric structures have improved nuclease resistance compared with un-cross linked structures (see abstract, page 2 entire text, p. 3 left col., p. 4 entire text, p. 5 left col., examples 1-3, pp. 6-7).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Uhlmann (US 2003/0139585) and Slattum (US 2004/0146867) as applied to claims 1-18, 21-32, 35-38, 41-49, 52-55 and 58-65 above, and further in view of Saba et al (USPN 5,082,934) and Cook et al (USPN 5,719,271) insofar as the claims are drawn to methods of inhibiting expression of a target gene in a cell in vitro comprising the administration of pharmaceutical compositions comprising double stranded oligonucleotides comprising complementary strands (sense and antisense) each comprising between 10 and 40 nucleotides, and which strands are covalently cross linked with one or more crosslinkers, including intrastrand crosslinkers, via psoralens, disulfides or crosslinked between heterocyclic bases, which oligomeric structures optionally comprise hairpins and optionally further comprise polyethylene glycol space spanning polymers, and which cross linked oligomeric structures have improved

nuclease resistance compared with un-crosslinked structures, and which compositions optionally further comprise cellular proteins identified as RNA-induced silencing complexes, leading to the degradation of intrinsic sequence unspecific degradation of target sequences.

Uhlmann and Slattum are relied upon as cited in the 102 rejections above.

The primary references of Uhlmann and Slattum do not teach crosslinked oligomeric structures comprising photoactive psoralens, nor do they teach intrastrand, multiple crosslinking between strands.

Saba et al (USPN 5,082,934) teach crosslinking between oligonucleotide strands using photoactive psoralen crosslinkers (see esp. co. 1-2, see also col. 3 and claims 1-10).

Cook et al (USPN 5,719,271) teach oligonucleotide strand crosslinking comprising space spanning groups, and including multiple, intra-strand crosslinking (see examples 12-15, col. 41-43, see also the abstract, col. 4, col. 5-8, 11, col. 48, claims 1-220.

It would have been obvious to one of skill in the art to crosslink oligonucleotide strands using photoactivatable crosslinkers including psoralens, because such means of crosslinking oligonucleotides had been routinely performed in the art as taught previously by Saba et al. One of ordinary skill in the art would have been motivated to utilize this method of crosslinking because it allows for the introduction of reactive crosslinking moieties into the oligonucleotides without interfering the nucleic acid's ability to hybridize to a target sequence, or to a self complementary strand as taught

previously by Saba et al. One of ordinary skill in the art would have expected that utilization of this means of chemical modification would render hybridizable oligonucleotides with enhanced nuclease resistance because crosslinking of nucleic acids had been taught previously to enhance oligonucleotide stability by many in the art, including Cook et al. One of ordinary skill in the art would have crosslinked the oligonucleotide strands at various intra-strand sites because Cook et al had previously taught this technique using various crosslinking reagents. One of ordinary skill would have been motivated to crosslink at multiple sites within the strand to optimize oligonucleotide structure and stability, as taught previously by Cook et al. One of ordinary skill in the art would have expected these forms of crosslinking oligonucleotides previously taught by Cook and Saba to be applicable to siRNA because the crosslinking technologies had been well known in the art and Uhlmann and Slattum both teach the crosslinking of siRNA molecules with enhanced target binding and stability using an array of crosslinking agents. Therefore the instant invention would have been obvious to one of ordinary in the art at the time the invention was made.

Conclusion

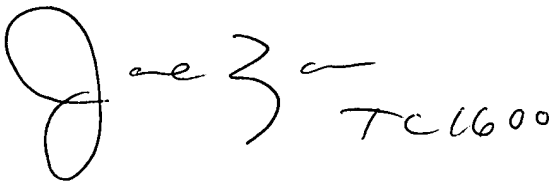
Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. 1.6(d)). The official fax telephone number for the Group is **571-273-8300**. NOTE: If Applicant *does* submit a paper by fax, the original

signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, can be reached on (571) 272-0811. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
3-16-06



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